

### **REMARKS**

Claims 2, 4 and 12-29 have been canceled without prejudice or disclaimer. Claims 1, 6, 8, 10, 30, 32, 34, 37, 39, 41, 43, 46, 48, 51, 53, 55, 58, 60, 62, 64, and 67-69 have been amended. Support for the amendments and new claims can be found throughout the specification and the claims as filed. This application presently contains claims 1, 3, 5-11 and 30-72. No new matter is added by these amendments. Applicant respectfully requests entry of the foregoing amendments.

#### ***Information Disclosure Statement***

Applicant thanks the Examiner for returning the initialed Form 1449 from the Information Disclosure Statement filed on February 6, 2006.

#### ***Withdrawn Objections and Rejections***

Applicant thanks the Examiner for indicating that the objections to claims 1, 3 and 5-11, and the rejection of claims 1, 3, and 5 under 35 U.S.C. § 112, second paragraph, have been overcome.

#### ***Rejections under 35 U.S.C. § 112, Second Paragraph (Indefiniteness)***

Claims 6, 8, 10, 30-35, 37, 39, 41, 43, 46, 48, 51, 53, 55, 58, 60, 62, 64, 67, and 69 stand rejected under 35 U.S.C. § 112, second paragraph for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Office Action at page 3. Applicant respectfully disagrees.

Claims 6 and 51 stand rejected as allegedly indefinite in the recitation of “the nucleic acid sequence attached to the primer has a length of 1 to 40 nucleotides.” In order to facilitate prosecution, claims 6 and 51 have been amended to recite “the nucleic acid sequence attached to

the primer has a length of 4 to 40 nucleotides.” In light of these remarks, Applicant submits that the grounds for the rejections of claims 6 and 51 for alleged indefiniteness have been rendered moot. Applicant therefore respectfully requests withdrawal of these rejections.

Claims 8, 32, 37, 41, 53, 58 and 62 are allegedly indefinite in the recitation of “the nucleic acid probe has a length of 25 to 60 nucleotides preferably approx. 50 nucleotides.” In order to facilitate prosecution, claims 8, 32, 37, 41, 53, 58 and 62 have been amended. Applicant submits that the grounds for the rejections of claims 8, 32, 37, 41, 53, 58 and 62 for alleged indefiniteness have been rendered moot. Applicant therefore respectfully requests withdrawal of these rejections.

Claims 10, 34, 39, 43, 46, 48, 55, 60, 64, 67 and 69 are allegedly indefinite in the use of a trademarked name. Applicant disagrees with the Office’s assertion that a person of ordinary skill in the art would not understand what is meant by the trademarked method “NASBA<sup>®</sup>,” but in order to facilitate prosecution, claims 10, 34, 39, 43, 46, 48, 55, 60, 64, 67 and 69 have been amended to define the trademarked name. Support for this amendment is found, for example, on page 1 of the specification. In light of these remarks, Applicant submits that the grounds for the rejections of claims 10, 34, 39, 43, 46, 48, 55, 60, 64, 67 and 69 for alleged indefiniteness have been rendered moot. Applicant therefore respectfully requests withdrawal of these rejections.

The Examiner asserts that claim 30 is allegedly indefinite in the recitation of “the nucleic acid sequence attached to the primer has a length of 1 to 40 nucleotides,” whereas claim 3, from which claim 30 depends allegedly does not contain a limitation of a sequence attached to a primer. In order to facilitate prosecution, Applicant has amended claim 30. Applicant submits that the grounds for the rejection of claim 30 for alleged indefiniteness have been rendered moot. Applicant therefore respectfully requests withdrawal of this rejection.

***Rejections under 35 U.S.C. § 103***

Claims 1, 3, 5-11 and 30-72 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Uijtewaal *et al.*, EP 0416572 A1, Leone *et al.*, Nucl. Acids Res. 26:2150-2155 (1998) and Heid *et al.*, Genome Research, 6:986-994 (1996). The office alleges that “[i]t would have been *prima facie* obvious to one of ordinary skill in the art to have used the real-time detection methods of Leone *et al.* and Heid *et al.* to detect ribozymes in transfected plants of Uijtewaal.” Office Action at page 6. The Office further alleges that motivation to combine these references is provided in Leone *et al.* (page 2155, last paragraph) and Heid *et al.* (page 992, first and second paragraphs). Office Action at pages 6-7. Applicant respectfully disagrees.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the applicant’s disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicant respectfully submits that the Office has failed to demonstrate the required suggestion or motivation to combine the reference teachings. The Examiner alleges that a motivation to combine can be found in particular paragraphs in Leone *et al.* (page 2155, last paragraph) and Heid *et al.* (page 992, first and second paragraphs). Office Action at page 6. Contrary to the Examiner’s allegations, the cited paragraphs describe the desirability of the existing methods of Leone *et al.* and Heid *et al.* These paragraphs do not suggest that additional modifications or materials should be added to these methods; instead, the methods are alleged to be sufficiently sensitive and robust in their current form to be used for a wide variety of applications beyond the specific results described. Indeed, the cited paragraphs fail to provide any motivation to modify or combine the teachings of these references at all. For this reason, the paragraphs cited by the Examiner actually teach away from the claimed invention.

More specifically, the Office has failed to demonstrate a motivation to modify the references in a manner consistent with the claims. For example, the Office has failed to demonstrate any motivation to modify the real-time detection methods of Leone *et al.* and Heid *et al.* through the use of a probe that does not adhere to the target but is split off and released by cleavage of a ribozyme. See, e.g., Specification at p. 10, lines 17-20; see also Figure 1.

Applicant submits that the Office has failed to demonstrate any motivation to modify or combine the teachings of Heid *et al.* Among its other disadvantages, the method of Heid *et al.* produces an equimolar signal, *i.e.*, only one probe molecule is split per amplified DNA target molecule per amplification cycle, which results in a comparatively weak signal. See, e.g., Specification at page 1, line 37 through page 2, line 10. At the very least, the Office has shown no motivation to modify the method of Heid *et al.* in a manner that results in an amplified signal (*e.g.*, through use of a ribozyme sequence that cleaves many probe molecules per each amplified target molecule, generating a stronger signal for each amplified target molecule). See, e.g., Specification at page 24, lines 12-17, and Figure 1.

The Office has similarly failed to demonstrate any motivation to modify or combine the teachings of Leone *et al.* The method of Leone *et al.* involves the use of “molecular beacons.” See, e.g., Leone *et al.*, paragraph bridging pages 2150-2151. As Leone *et al.* admits, this technology has the disadvantage that the “molecular beacon” probe can compete with the amplification by hybridizing to the amplicon, thus interfering with quantitation. See, e.g., Leone *et al.* at page 2152, column 2, second full paragraph, and page 2153, Figures 5-6; see also Specification at page 3, lines 12-23. At the very least, the Office has shown no motivation to modify the method of Leone in a manner that eliminates the problem of probe competing with amplification. In contrast, the present application states that “there is no possible competition between detection and amplification as the probe – an RNA substrate probe – does not adhere to the target but is split off and released, whereby a detectable signal is generated.” Specification at p. 10, lines 17-20; see also Figure 1.

Finally, the Office has failed to provide any motivation to modify or combine the teachings of Leone *et al.* and Heid *et al.* with those of Uijtewaal *et al.* Applicant provides herewith for the Examiner’s consideration an English translation of Uijtewaal *et al.* See Exhibit A. As the Examiner admits, Uijtewaal *et al.* does not teach real-time detection of nucleic acid

molecules. Office Action at page 5. Instead, Uijtewaal *et al.* teaches that “ribozymes can attack plant RNA coding for maturation enzymes, and so can be used to influence the maturation processes in plants.” Uijtewaal *et al.* at page 2, lines 21-22. Uijtewaal *et al.* simply demonstrates, in part, that certain tomatoes transgenic for ribozyme sequences in genes coding for maturation enzymes can exhibit delayed maturation. *See, e.g.,* Uijtewaal *et al.* page 7, lines 44-48.

There is no logical connection between the teachings of Uijtewaal *et al.* (regarding alteration of the maturation of plants) and the teachings of Leone *et al.* and Heid *et al.* (regarding real-time quantitation of nucleic acids). As such, there is no motivation to combine these teachings. Furthermore, for the same reason, a person of ordinary skill in the art would have no reasonable expectation of success in combining the teachings of Uijtewaal *et al.* with those of Leone *et al.* and Heid *et al.*

Finally, a prima facie case of obviousness requires that the prior art reference, or references when combined, teaches or suggests all of the claim limitations. Whatever else Uijtewaal *et al.*, Leone *et al.*, and Heid *et al.* teach, these references do not teach or suggest the processes of claims 1 or 3. At the very least, Uijtewaal *et al.*, Leone *et al.*, and Heid *et al.* do not teach or suggest “carrying out the amplification in the presence of an excess of a nucleic acid probe which contains the sequence motif 5'-CUGANGA-3' (motif B), a reporter molecule and a quencher molecule attached to each probe molecule.”

For at least the foregoing reasons, Applicant respectfully requests withdrawal of the rejections of claims 1, 3, 5-11 and 30-72 under 35 U.S.C. § 103(a) for purported unpatentability over Uijtewaal *et al.*, Leone *et al.*, and Heid *et al.*

The presently pending claims are believed to be in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. The Examiner is respectfully requested to contact Applicant's undersigned representative at 202.942.5512 to address any unresolved issues remaining in this application.

Respectfully submitted,

A handwritten signature in black ink that reads "Rachel L. Adams". The signature is written in a cursive, flowing style.

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Date: July 20, 2006

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